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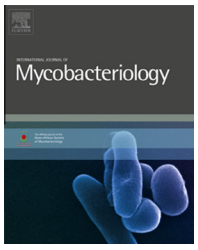

Drug development: The cell wall as a drug target

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The complex and essential cell wall of *Mycobacterium tuberculosis* represents a plethora of new and old drug targets that collectively form an apparent mycobacterial "Achilles' heel". The mycolic acids are long-chain α-alkyl-β-hydroxy fatty acids ($C_{70–90}$), which are unique to mycobacterial species, forming an integral component of the mycolyl–arabinogalactan–peptidoglycan complex. Their apparent uniqueness to the *M. tuberculosis* complex has rendered components of mycolic acid biosynthesis as powerful drug targets for specific tuberculosis (TB) chemotherapy. Here, I will discuss a contribution to TB drug discovery by deconvolution of the inhibitory mechanisms of a number of antitubercular compounds targeting mycolic acid biosynthesis. I will begin with the early days, elucidating the mode of action of ethionamide [1] and thiolactomycin [2], each targeting two separate components of the fatty acid synthase II (FAS-II) pathway. I will further discuss the recently discovered tetrahydropyrazo[1,5-*a*]pyrimidine-3-carboxamide compounds [3] which selectively target the essential, catalytically silent *M. tuberculosis* EchA6, providing a crucial lipid shunt between β-oxidation and FAS-II and supplying lipid precursors for essential mycolate biosynthesis. Finally, I will discuss the recent discovery of the mode of action of the indazole sulfonamides [4], inhibiting *M. tuberculosis* KasA by, a completely novel inhibitory mechanism.

Conflict of interest

The author declared that there is no conflict of interest.

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